GLI STUDI RETROSPETTIVI IN EMATOLOGIA: PRO E CONTRO

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Clinical studies – the evidence 'hierarchy'

Meta-analyses/systematic reviews of well-designed and conducted studies

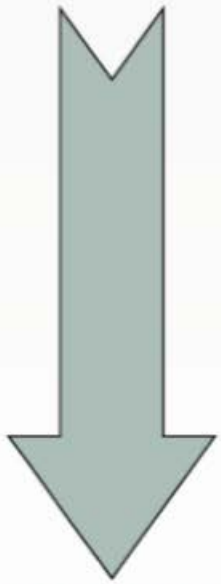
Randomised controlled trial (RCT)

Cohort study
Case-control study

Cross-sectional study

Case series/case note review

'Expert' opinion



Experimental/observational studies

- Experimental study: Investigator intervenes in the care of the patient in a pre-planned way and records the outcome
  - Randomised controlled trials; laboratory studies
- Observational study: Investigator does not intervene in the care of the patient, but simply records what happens
  - Cohort studies; case-control studies

Randomised controlled trials (RCTs)

- Experimental study in which treatments are allocated randomly to patients using process known as randomisation
- Ensures that characteristics of those in each treatment arm are broadly similar (any differences are due to chance)
- If there are differences in outcome, these are unlikely to be explained by baseline differences between the groups

Limitations of RCTs

- Only possible if there is an 'intervention' to which people are willing to be randomised
- Patients in RCTs may be unrepresentative of clinic population, and management may be different – outcomes may differ from what would be expected
- May be short (48 weeks)
- May focus on two or three main treatment comparisons
- May focus on short-term surrogate marker changes rather than on longer-term clinical endpoints

Randomised Controlled Trials

Typically assess **efficacy:** defined as the performance of an intervention under ideal and controlled circumstances

Observational Trials

Generally investigate **effectiveness:** defined as the performance of an intervention under 'real-world' conditions

Differences between efficacy and effectiveness studies

	Efficacy Studies	Effectiveness studies
Question	Does the intervention work under ideal circumstance?	Does the intervention work in real-world practice?
Setting	Resource-intensive 'ideal setting'	Real-world everyday clinical setting
Study Population	Highly selected, homogenous population. Several exclusion criteria	Heterogeneous population Few to no exclusion criteria
Providers	Highly experienced and trained	Representative usual providers
Intervention	Strictly enforced and standardized No concurrent interventions	Applied with flexibility Concurrent interventions and cross-over permitted

- **Randomized Controlled Trials (RCTs), are recognized as the ‘gold standard’ for establishing efficacy and provide evidence for Therapeutic Guidelines**

- **Observational Studies have an important and increasing role to play in the evaluation of epidemiology and burden of disease, treatment patterns, compliance, persistence, and health outcomes of different treatments.**

STUDI RETROSPETTIVI

VANTAGGI

1) DI BREVE DURATA
2) RELATIVAMENTE ECONOMICI
3) ADATTI ALLE MALATTIE RARE
4) PROBLEMI ETICI MINIMI
5) SOGGETTI NON NECESSARIAMENTE VOLONTARI
6) POCHI SOGGETTI RICHIESTI
7) NESSUN PROBLEMA DI COESIONE DI GRUPPO
8) ADATTI ALLO STUDIO DI MALATTIE INDOTTE DA FARMACI
9) SI PU0' IDENTIFICARE PIU' DI UN FATTORE DI RISCHIO

SVANTAGGI

1) POSSIBILITÀ DI ERRORI SISTEMATICI NELLA SELEZIONE DEL GRUPPO DI CONTROLLO
2) RICORDI VIZIATI
3) IMPOSSIBILE DETERMINARE INCIDENZA
4) RISCHIO RELATIVO APPROSSIMATO

BREVE DURATA ?

Cancer Treat Rev. 2017 Feb;53:38-46. doi: 10.1016/j.ctrv.2016.11.015. Epub 2016 Dec 22.

Rituximab: 13 open questions after 20years of clinical use.

Pavanello F[1], Zucca E[1], Ghielmini M[2].

Author information

optimal schedule, the interaction with chemotherapy, as well as predictive factors for response rate and duration. Despite being very well tolerated, the question of its long term side effects and the risks of the administration near to a pregnancy have only recently been addressed. Also the indications are still not all clear: rituximab induces remissions as a single agent and improves the effect of chemotherapy, but its use as maintenance or as a substitute for watch and wait is still debated. Also, it is still unclear if its efficacy derives at least partly by reducing the risk of histological transformation in indolent NHL and reducing the risk of CNS relapse in aggressive NHL. Finally, despite of 20years of research, it is still unclear if rituximab can be efficiently substituted by biosimilars or new anti-CD20 antibodies. In this review we address all these questions and analyze the literature addressing these aspects.

NESSUN PROBLEMA DI COESIONE DEL GRUPPO ?

bjh research paper

A retrospective study on the management of patients with rituximab refractory follicular lymphoma

Philippe Solal-Céligny,[1] Pierre Leconte,[2] Aurélie Bardet,[2] Juana Hernandez[2] and Xavier Troussard[3]

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Received 16 June 2017; accepted for

Summary

Given that there are currently no clear recommendations regarding therapeutic options for rituximab refractory/relapsed follicular lymphoma patients, this study aimed to describe the real-life management of patients with refractory follicular lymphoma after systemic rituximab-containing regimens (rFL), and rFL patient characteristics. In this retrospective, national, multicentre study, descriptive analyses were mainly performed according to rituximab-containing regimen at rFL diagnosis [rituximab

P. Solal-Céligny *et al*

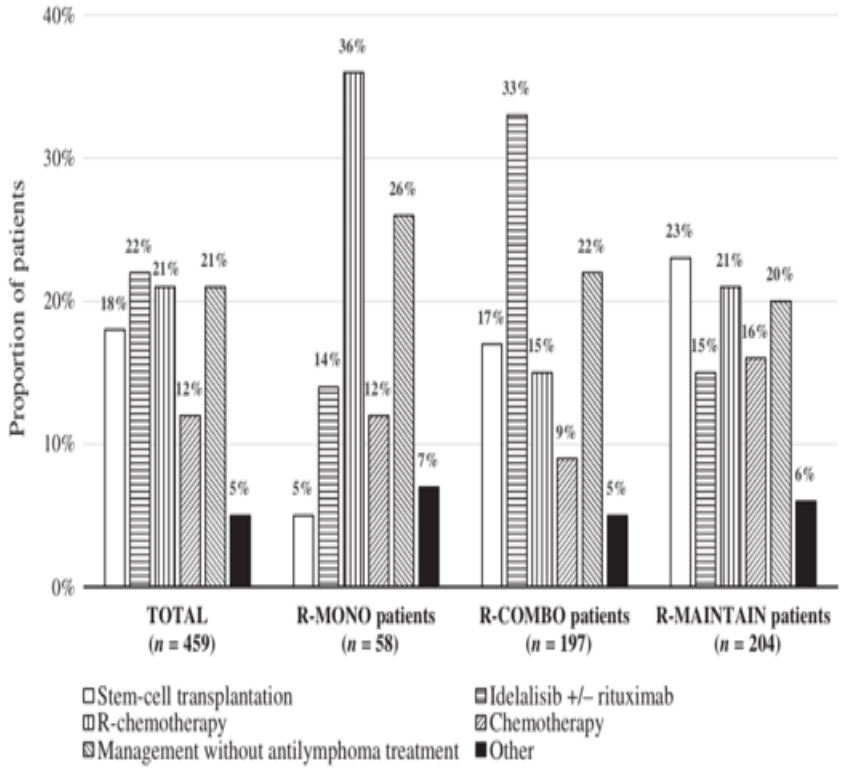

Fig 1. Therapeutic management of patients after rFL diagnosis, according to prior FL therapy (study primary endpoint). FL, follicular lymphoma; R-COMBO, refractory to rituximab + chemotherapy; R-MAINTAIN, refractory to ongoing rituximab maintenance; R-MONO, refractory to rituximab monotherapy; R, rituximab; rFL, follicular lymphoma refractory to rituximab.

Table II. Therapeutic management of patients after rFL diagnosis, according to patients and disease characteristics – R-COMBO patients (n = 197) and R-MAINTAIN patients (n = 204).

	Stem cell transplantation n = 33	Idelalisib ± R n = 65	R-Chemotherapy n = 30	Chemotherapy n = 17	Management without anti-lymphoma treatment n = 43	Other n = 9
R-COMBO patients (n = 197)						
Therapeutic strategy according to patient age, n (%)						
<65 years (n = 83)	28 (33·7)	29 (34·9)	12 (14·5)	5 (6·0)	7 (8·4)	2 (2·4)
≥65 years (n = 114)	5 (4·4)	36 (31·6)	18 (15·8)	12 (10·5)	36 (31·6)	7 (6·1)
Therapeutic strategy according to number of treatment lines at rFL diagnosis, n (%)						
1st line (n = 54)	13 (24·1)	4 (7·4)	15 (27·8)	9 (16·7)	12 (22·2)	1 (1·9)
2nd or 3rd line (n = 143)	20 (14·0)	61 (42·7)	15 (10·5)	8 (5·6)	31 (21·7)	8 (5·6)
Therapeutic strategy according to the patient age and number of treatment lines at rFL diagnosis, n (%)						
<65 years						
1st line (n = 24)	11 (45·8)	1 (4·2)	7 (29·2)	4 (16·7)	1 (4·2)	0
2nd or 3rd line (n = 59)	17 (28·8)	28 (47·5)	5 (8·5)	1 (1·7)	6 (10·2)	2 (3·4)
≥65 years						
1st line (n = 30)	2 (6·7)	3 (10·0)	8 (26·7)	5 (16·7)	11 (36·7)	1 (3·3)
2nd or 3rd line (n = 84)	3 (3·6)	33 (39·3)	10 (11·9)	7 (8·3)	25 (29·8)	6 (7·1)
	n = 46	n = 30	n = 43	n = 33	n = 40	n = 12
R-MAINTAIN patients (n = 204)						
Therapeutic strategy according to patient age, n (%)						
<65 years (n = 86)	40 (46·5)	10 (11·6)	11 (12·8)	12 (14·0)	11 (12·8)	2 (2·3)
≥65 years (n = 118)	6 (5·1)	20 (16·9)	32 (27·1)	21 (17·8)	29 (24·6)	10 (8·5)
Therapeutic strategy according to number of treatment lines at rFL diagnosis, n (%)						
1st line (n = 132)	41 (31·1)	9 (6·8)	38 (28·8)	19 (14·4)	19 (14·4)	6 (4·5)
2nd or 3rd line (n = 72)	5 (6·9)	21 (29·2)	5 (6·9)	14 (19·4)	21 (29·2)	6 (8·3)
Therapeutic strategy according to patient age and number of treatment lines at rFL diagnosis, n (%)						
<65 years						
1st line (n = 63)	35 (55·6)	0	10 (15·9)	8 (12·7)	8 (12·7)	2 (3·2)
2nd or 3rd line (n = 23)	5 (21·7)	10 (43·5)	1 (4·3)	4 (16·7)	3 (13·0)	0
≥65 years						
1st line (n = 69)	6 (8·7)	9 (13·0)	28 (40·6)	11 (15·9%)	11 (15·9)	4 (5·8)
2nd or 3rd line (n = 49)	0	11 (22·4)	4 (8·2)	10 (20·4%)	18 (36·7)	6 (12·2)

R-COMBO, refractory to rituximab + chemotherapy; R-MAINTAIN, refractory to ongoing rituximab maintenance; R, rituximab; rFL, follicular lymphoma refractory to rituximab.

Table III. Decision-making factors of the post-rFL strategies (multinomial regressions) compared to R-chemotherapy choice.

Significant parameters ($P \leq 0{\cdot}05$)	Post-rFL strategies [OR (95% CI)]				
	Management without anti-lymphoma treatment	Chemotherapy only	Idelalisib +/- rituximab	Rituximab / non-standard treatment	Stem cell transplantation
Age at rFL diagnosis (≥ 65 vs. <65 years)	1·1 (0·5–2·4)	0·8 (0·4–1·8)	0·5 (0·2–1·1)	1·4 (0·4–4·1)	**0·1 (0·0–0·2)**
Body mass index (<25·0 vs. ≥25·0 kg/m^2)	**2·2 (1·0–4·4)**	1·6 (0·7–3·5)	1·8 (0·8–3·6)	1·6 (0·5–4·3)	0·6 (0·2–1·3)
Number of treatment lines at rFL diagnosis (2nd or 3rd line vs. 1st line)	**5·9 (2·8–12·0)**	**3·6 (1·6–8·0)**	**23·4 (10·4–52·4)***	**7·4 (2·6–20·7)**	1·5 (0·6–3·4)
ECOG performance score (>2 vs. ≤2)	**21·4 (2·5–180·1)**	5·3 (0·4–58·1)	3·4 (0·2–43·1)	NA (0)	2·5 (0·1–46·3)
FLIPI score (3 vs. <3)	0·9 (0·4–1·8)	**0·4 (0·2–1·0)**	0·9 (0·4–1·8)	**0·2 (0·0–0·6)**	**3·0 (1·3–6·3)**
Physician specialty (non-haematologist vs. haematologist)	**4·0 (1·9–8·1)**	**7·2 (3·2–15·9)**	**5·4 (2·6–11·2)**	1·9 (0·6–5·6)	1·6 (0·7–3·5)

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; NA, not available; OR, odds ratio; rFL, follicular lymphoma refractory to rituximab. Bold values refer to signifcant OR, i.e. 95% CI does not contain 1.

*Example of results interpretation: compared to the post-rFL prescription of an rituximab-chemotherapy regimen, the patients with at least 2 previous treatment lines (*versus* 1 line) were 23·4 times more likely to receive idelalisib ± rituximab.

heterogeneity of post-rFL therapeutic strategies as observed in this French study makes it difficult to conduct clinical trials assessing new treatments in comparison with a consensual comparator and to refine the current recommendations for rFL patients' management. In this context, the interest of this study conducted in a real-life setting is to

POCHI SOGGETTI RICHIESTI ?

The Risk of Transformation of Follicular Lymphoma "Transformed" by Rituximab. The Aristotle Study promoted by the European Lymphoma Institute.

M. Federico(*), **D. Caballero**, L. Marcheselli, V. Tarantino, C. Sarkozy, A. Lopez Guillermo, M. Wondergem, E. Kimby, C. Rusconi, E. Zucca, S. Montoto, M. Gomes da Silva, I. Aurer, E. Paszkiewicz-Kozik, G. Cartron, F. Morschhauser, M. Alcoceba, M. Chamuleau, S. Lockmer, C. Minoia, D. Issa, S. Alonso, L. Conte, G. Salles, and **B. Coiffier**

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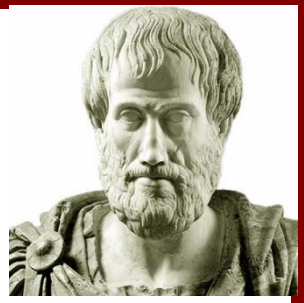
Study Population



Submitted **n = 9172**

Excluded:

NA	n = 1255
tFL at diagnosis = 22	n
Lack of date dia./rel.	n = 49
Dia. <1997 or >2013	n = 441
	N = **1767** (19%)

Assessable **n = 7405** (81% of

Any Event **n = 4531** (61% of assessable)

Biopsy Proven **n = 792** (17% of any event)

tFL **n=439**

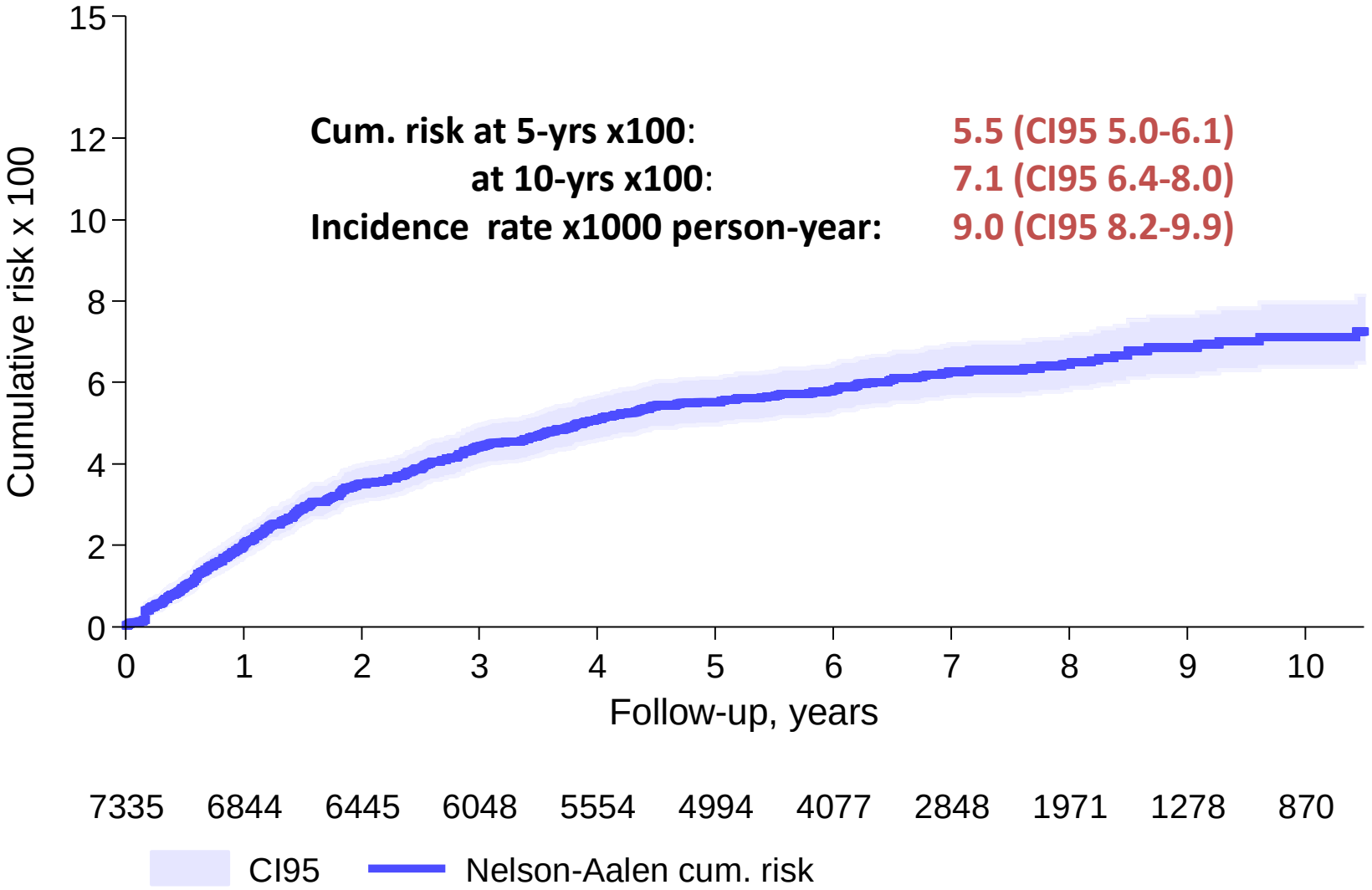
Federico et al. Abs #105. ICML 2017.

Study population

Group	Submitted	Assessable	tFL	Median time to tFL
	n (%)			
Croatia	225 (2)	198	2	32 mo
FIL	2066 (24)	749	49	22 mo
GELTAMO	1801 (19)	1773	126	27 mo
IPO Lisboa	244 (3)	243	16	32 mo
PHAROS (NL)	1569 (17)	1549	80	11 mo
Bart (UK)	251 (3)	251	47	22 mo
Sweden	550 (6)	544	12	30 mo
IOSI (SUI)	383 (4)	195	12	24 mo
LYSA	1976 (21)	1803	91	14 mo
POLAND	107 (1)	100	4	24 mo
Total	**9172 (100)**	**7405 (81)**	**439**	**19 mo**

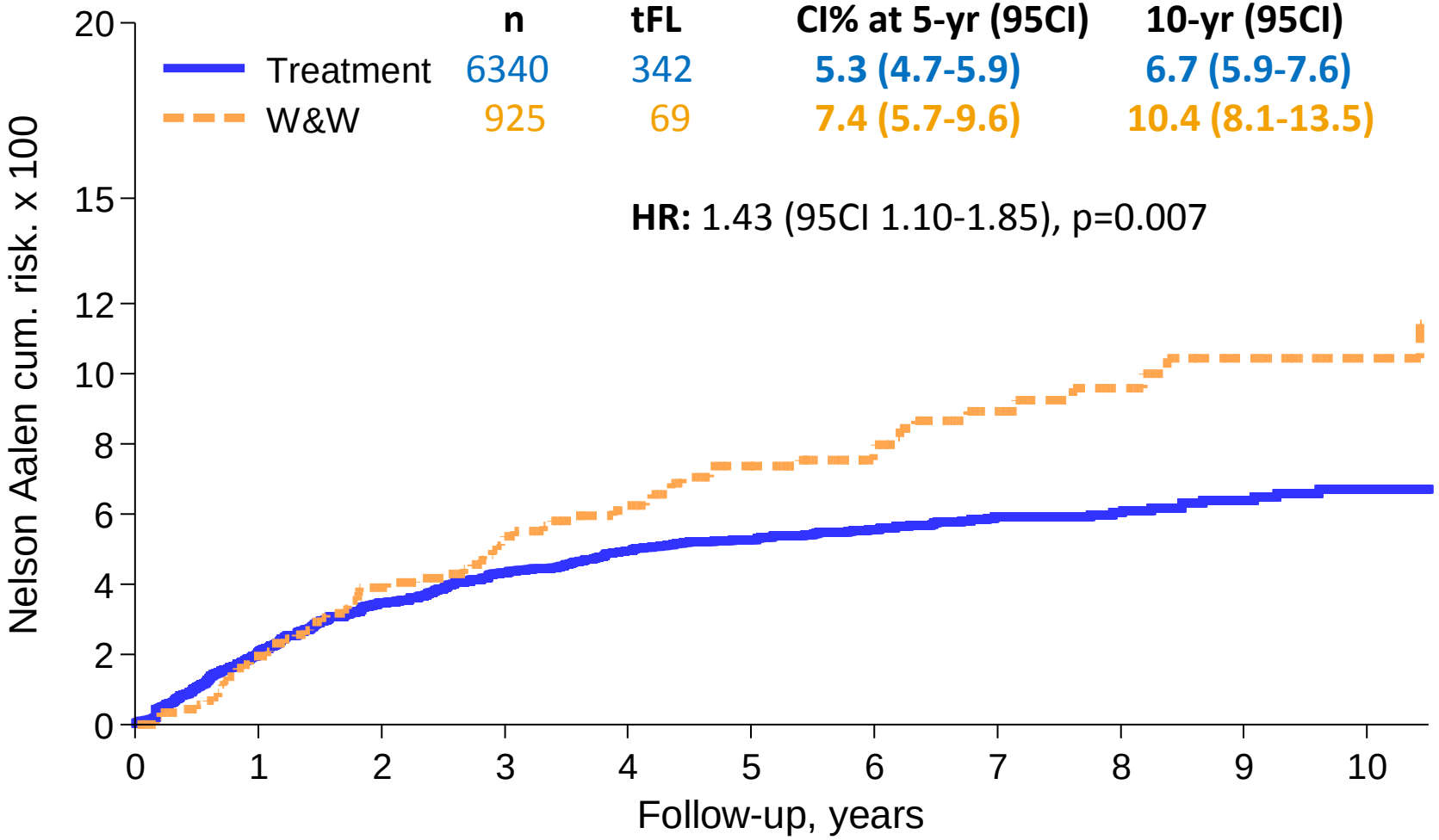
Federico et al. Abs #105. ICML 2017.

Cumulative incidence of biopsy proven transformation as first event (n= 413/7335)



Federico et al. Abs #105. ICML 2017.

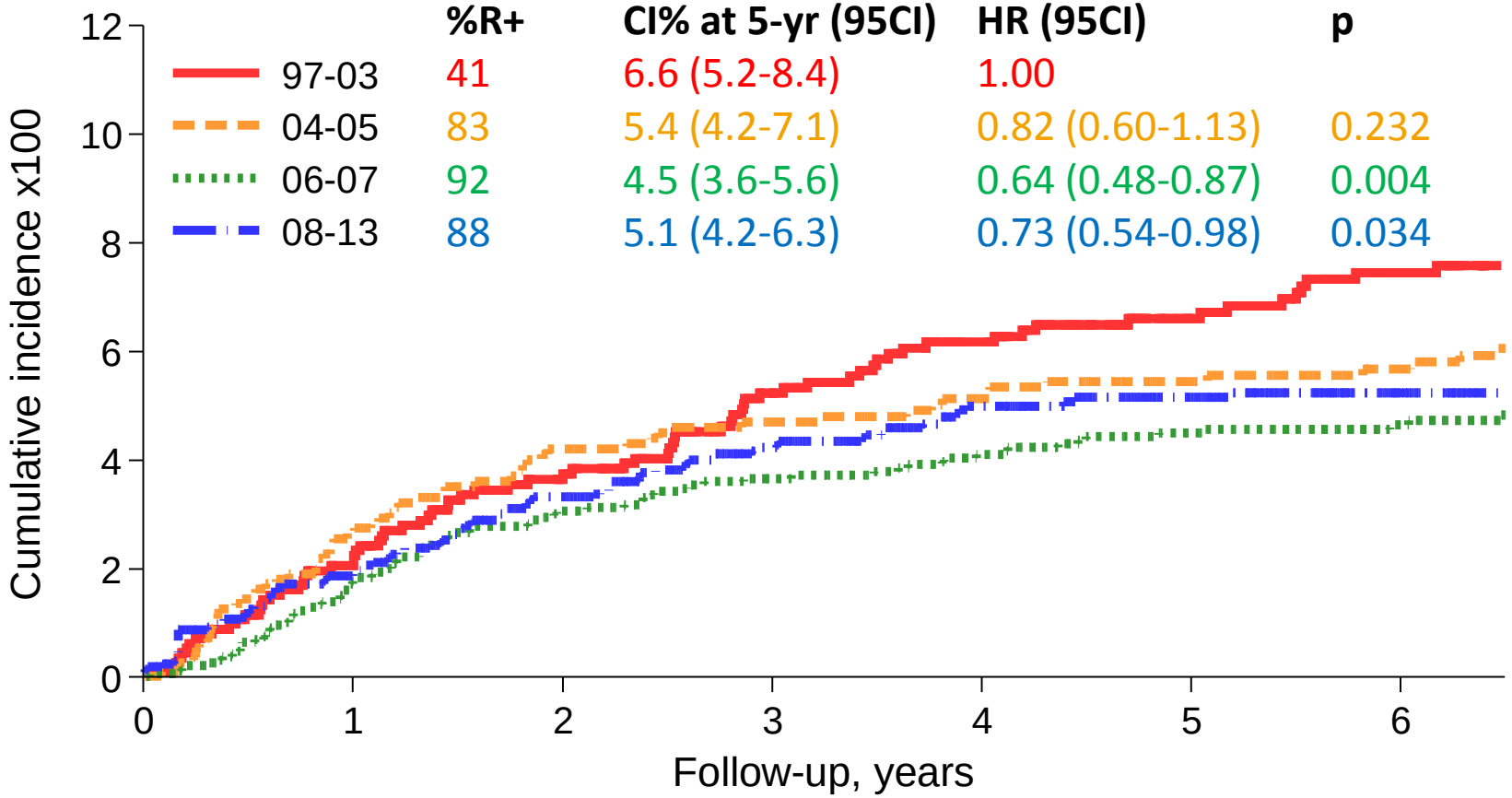
Cumulative incidence by therapeutic approach (n= 7335)



Treat	6340	5942	5603	5271	4863	4368	3583	2487	1702	1077	740
W&W	925	845	789	729	651	591	467	343	256	192	124

Federico et al. Abs #105. ICML 2017.

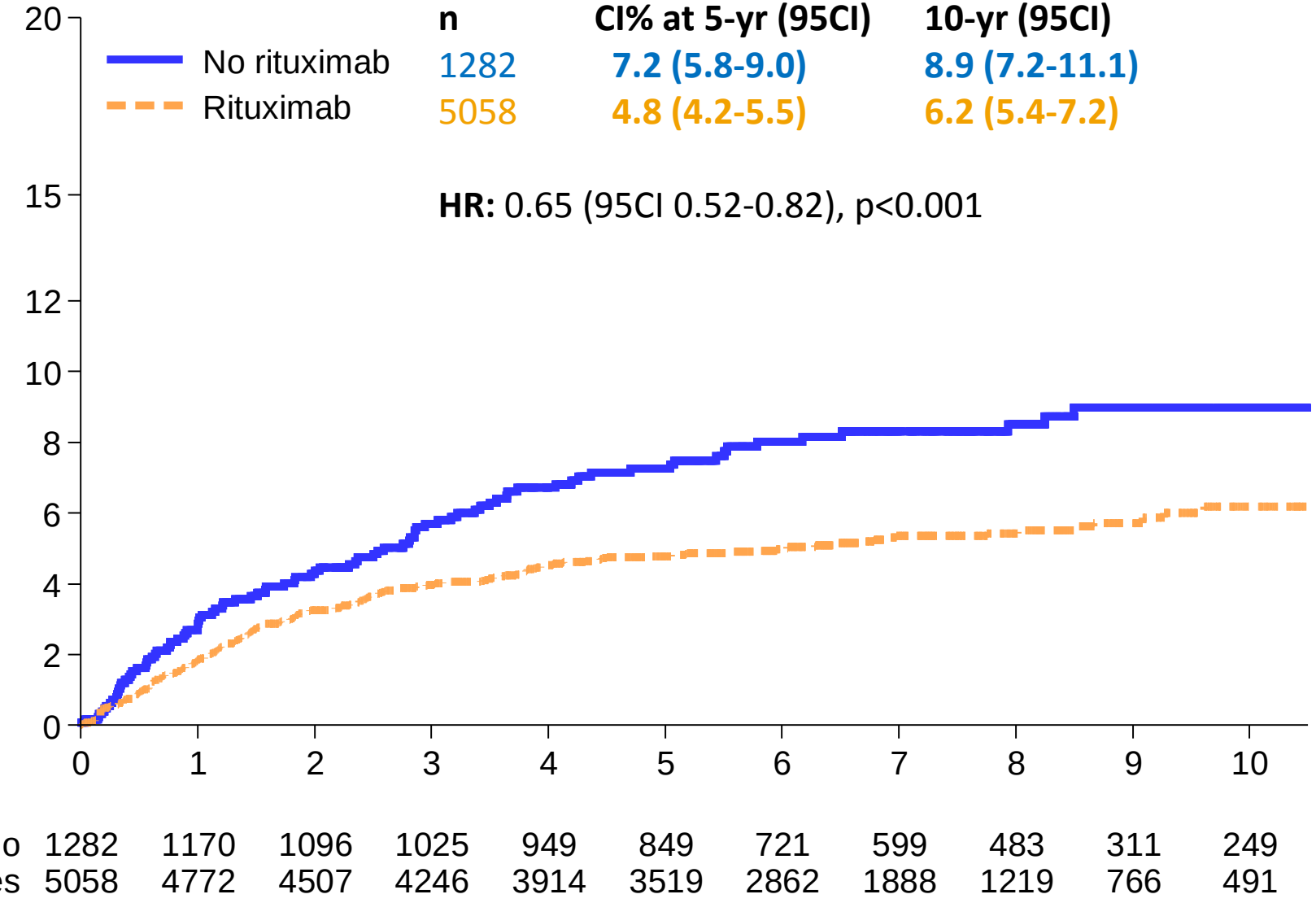
Cumulative Incidence by period of diagnosis



97-03	1161	1092	1036	982	936	865	792
04-05	1149	1060	1007	973	925	885	830
06-07	1931	1826	1720	1633	1554	1478	1221
08-13	2099	1964	1840	1683	1448	1140	740

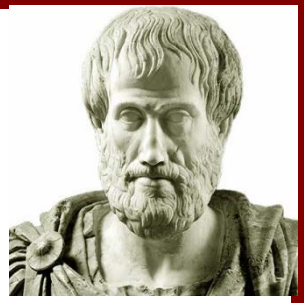
Federico et al. Abs #105. ICML 2017.

Cumulative Incidence by Rituximab use (n= 6340)

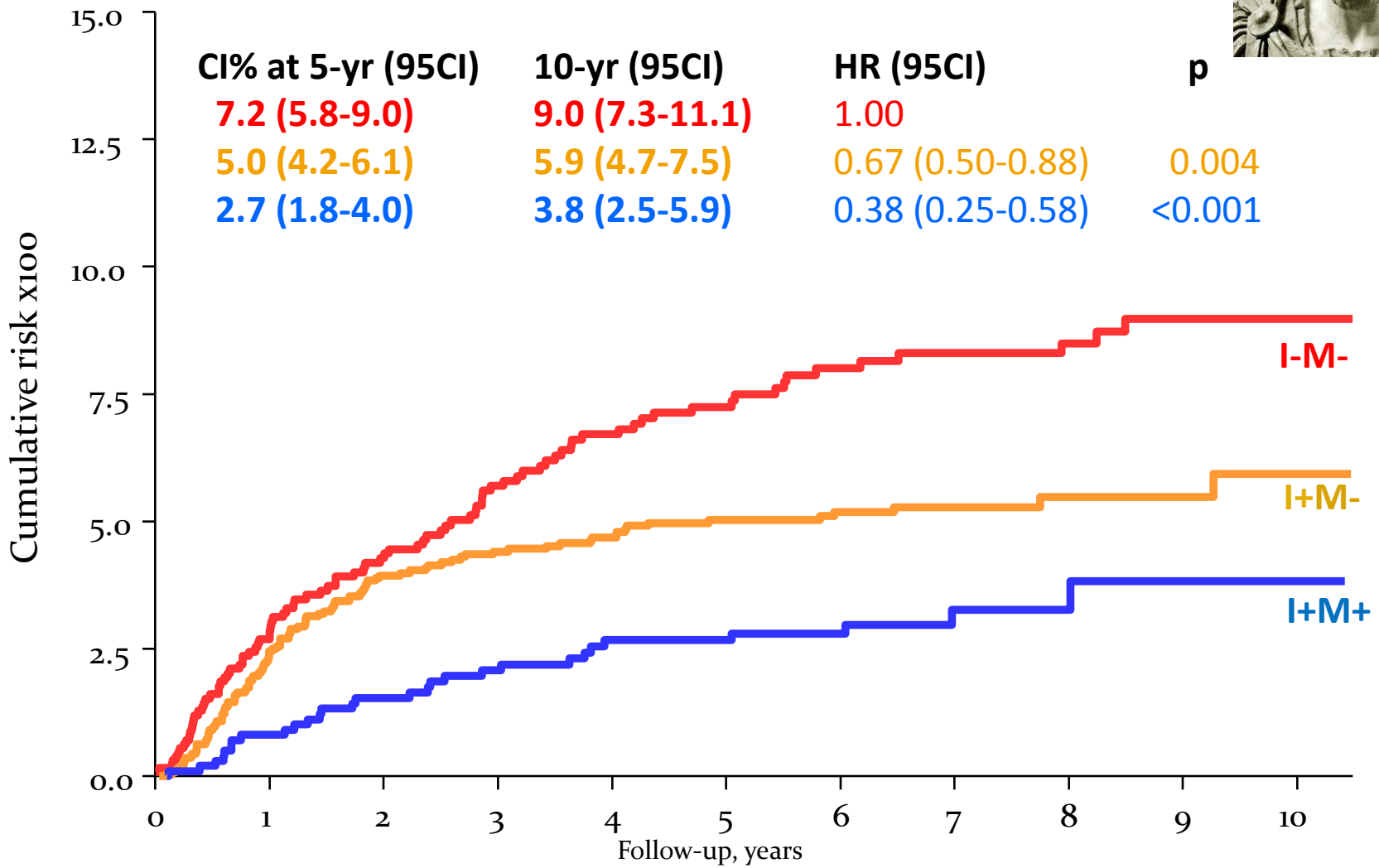


Federico et al. Abs #105. ICML 2017.

Cumulative Incidence by Rituximab exposure

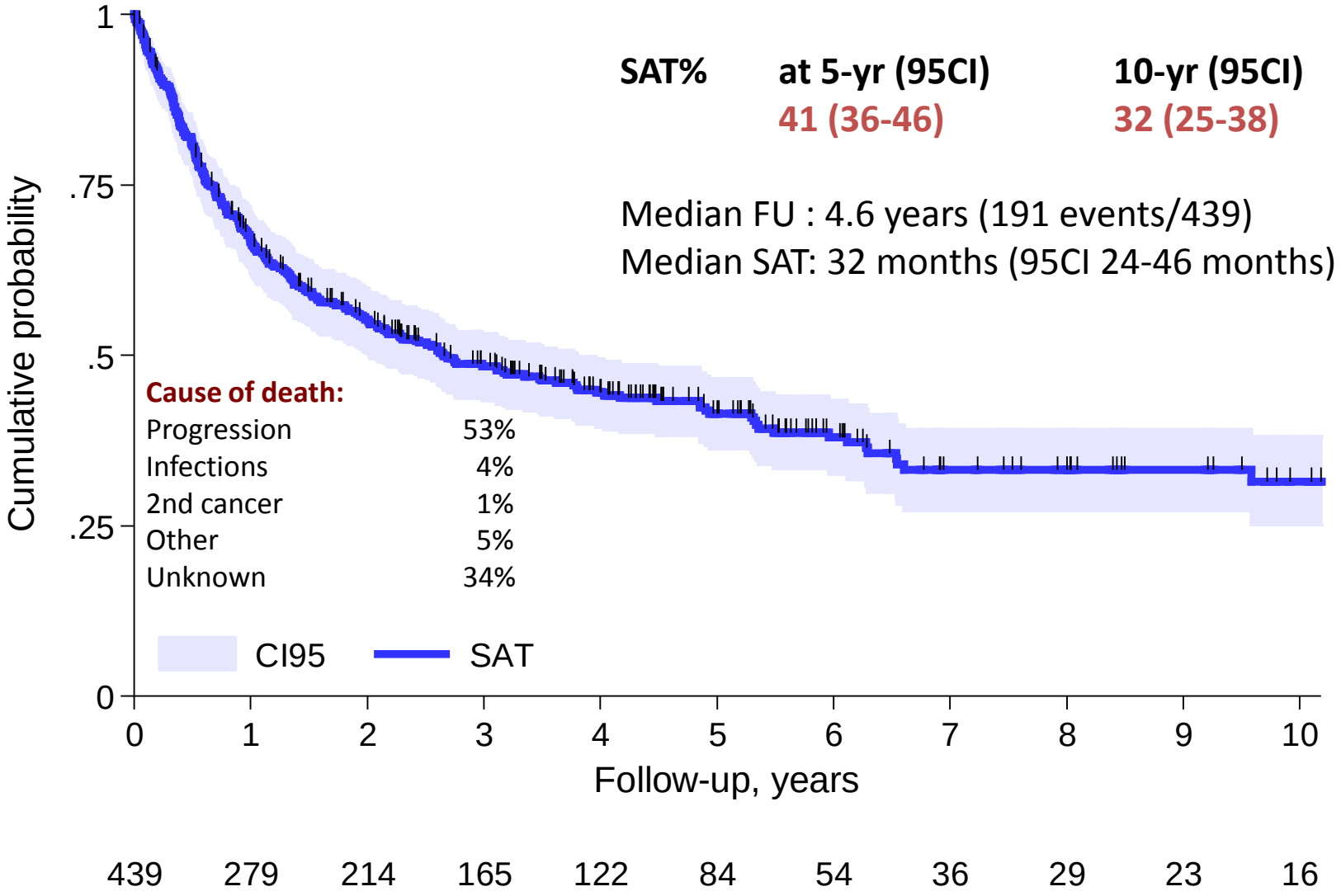


CI% at 5-yr (95CI)	10-yr (95CI)	HR (95CI)	p
7.2 (5.8-9.0)	9.0 (7.3-11.1)	1.00	
5.0 (4.2-6.1)	5.9 (4.7-7.5)	0.67 (0.50-0.88)	0.004
2.7 (1.8-4.0)	3.8 (2.5-5.9)	0.38 (0.25-0.58)	<0.001



I-M-	1282	1170	1096	1025	949	849	721	599	483	311	249
I+M-	2260	2082	1957	1864	1758	1626	1309	783	427	254	149
I+M+	993	976	942	891	823	763	598	339	178	55	14

Survival after tFL (SAT) [n=439]



Federico et al. Abs #105. ICML 2017.

Conclusions

- Despite the potential limitation of a retrospective analysis, the Aristotle study suggests that the risk of HT as first event has been significantly reduced by the introduction of Rituximab
- Treatment of tFL is still challenging; however the outcome seems today "less dismal and cathastrophic" than usually reported in the Literature

Federico et al. Abs #105. ICML 2017.

To the editor:

Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy

Ajay K. Gopal,[1] Brad S. Kahl,[2] Christopher R. Flowers,[3] Peter Martin,[4] Stephen M. Ansell,[5] Esteban Abella-Dominicis,[6] Brian Koh,[6] Wei Ye,[6] Paul M. Barr,[7] Gilles A. Salles,[8] and Jonathan W. Friedberg[7]

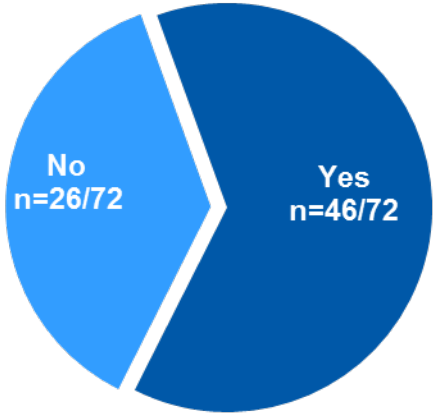
[1]Division of Medical Oncology, Department of Medicine, University of Washington, Clinical Research Division, Fred Hutchinson Cancer Research Center, and Seattle Cancer Care Alliance, Seattle, WA; [2]Oncology Division, Department of Medicine, University of Wisconsin–Madison, Madison, WI; [3]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; [4]Division of Hematology and Oncology, Department of Medicine, Weill Cornell Medicine, New York, NY; [5]Division of Hematology, Mayo Clinic, Rochester, MN; [6]Gilead Sciences, Inc., Foster City, CA; [7]Department of Medicine, James P. Wilmot Cancer Center, University of Rochester, Rochester, NY; and [8]Department of Hematology, University Claude Bernard Lyon 1, Hospices Civils de Lyon, Pierre-Benite, France

Methods

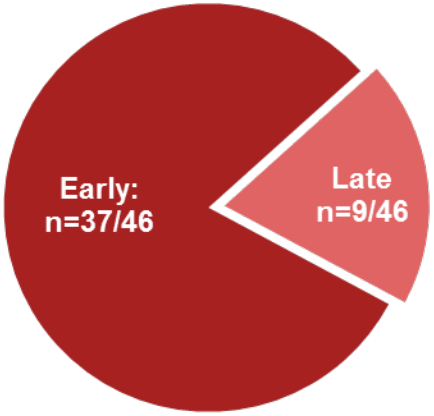
- Retrospective subgroup analysis of data from the Phase 2 trial of idelalisib in patients with FL (Study 101-09; NCT01282424)
- Population
  - Patients with FL who experienced early POD and received first-line (1L) CIT
  - Early POD defined as initiation of 2nd-line chemotherapy within 24 mos of initiating 1L CIT

Study Population

1L Chemoimmunotherapy



Progression of Disease



Of pts with FL who received 1L CIT, 37 of 64 experienced early POD

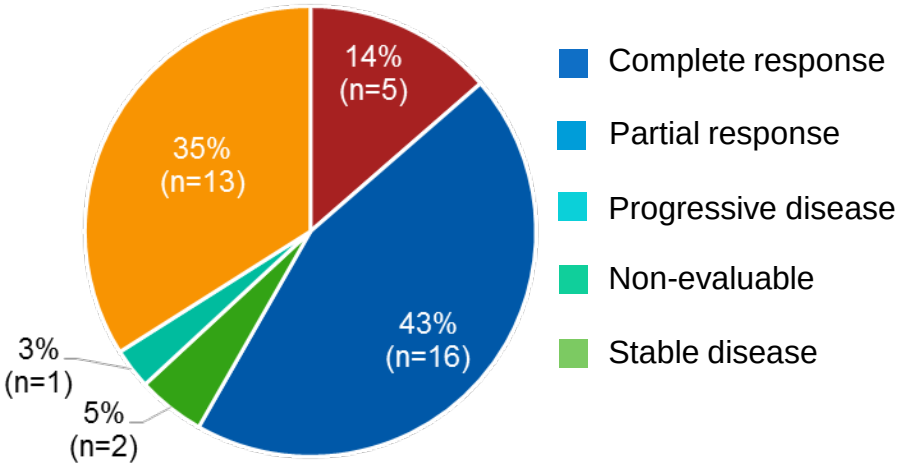
Demographics and Baseline Characteristics

Patients with Early POD		N=37
Median age, y (range)		64 (33–84)
Female, n (%)		18 (49)
Histologic Grade, n (%)	1 or 2	33 (89)
	3A	4 (11)
FLIPI score ≥3, n (%)		21 (57)
Mean no. of prior therapies (SD; range)		3.4 (1.4; 2–8)
Prior therapy, n (%)	R-CHOP	21 (57)
	BR	7 (19)
	R-CVP	5 (14)
Mean intertreatment interval, mos (SD)	1st and 2nd	12.5 (6.1)
	2nd and 3rd	9.7 (9.3)
	3rd and 4th	11.9 (12.0)*
	4th and 5th	11.8 (7.6)†
Median time to IDL, mo (range)‡		30.3 (8.9–94.7)

*n=24 (65%); †n=15 (41%); ‡Measured from time of initiation of 1st-line therapy; no patient received idelalisib as 2nd-line therapy. BR, bendamustine-rituximab; CIT: chemoimmunotherapy; FLIPI, FL International Prognostic Index; R-CVP, rituximab-cyclophosphamide-prednisone.

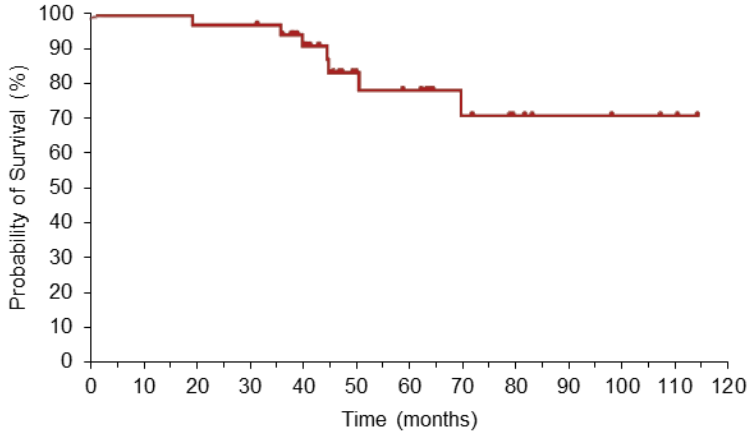
‡

Study Results



- Median (95% CI) DOR was 11.8 months (3.8, NE)

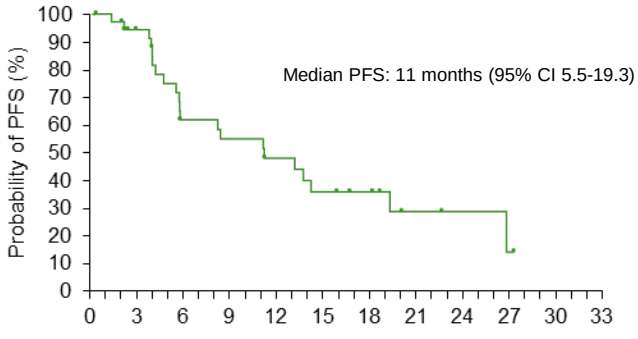
Overall Survival From Initiation of 1st-line Treatment



Total
n at risk (events) 37 (0) 37 (0) 36 (1) 35 (1) 25 (3) 16 (6) 15 (6) 10 (7) 6 (7) 4 (7) 3 (7) 1 (7) 0 (7)

- Median OS following initiation of 1st-line CIT was not reached

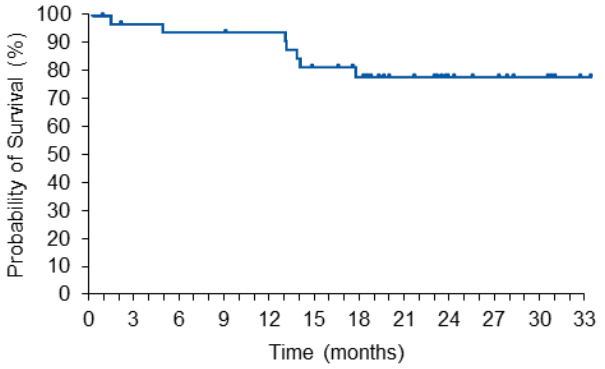
Progression-Free Survival From Initiation of Idelalisib



Total
n at risk (events) 37 (0) 30 (2) 18 (12) 16 (14) 12 (16) 9 (19) 7 (19) 3 (20) 2 (20) 1 (21) 0 (21) 0 (21)

- 2-yr PFS (±SE) following initiation of idelalisib was 29% (± 10%)

Overall Survival From Initiation of Idelalisib



Total
n at risk (events) 37 (0) 34 (1) 33 (2) 32 (2) 32 (2) 27 (6) 20 (7) 16 (7) 8 (7) 5 (7) 2 (7) 0 (7)

- Median OS following initiation of idelalisib was not reached
- 2-yr OS (±SE) following initiation of idelalisib was 79% (±7%)

Gopal A, ASH, 2015, #2744

When interpreting the promising efficacy results from this analysis, caution should be exercised when comparing these results to registry-based outcomes.[2] It is likely that patients reported here represent only a subset of patients with treatment failure within 24 months and may not fully reflect the characteristics of this population.

STUDI OSSERVAZIONALI PROS

- Contribuiscono alla comprensione di rischi e benefici degli interventi sanitari, compresi quelli farmacologici
- Se esistono eventi avversi associati ai farmaci e se il rischio varia nel tempo
- Sono utili a prendere decisioni informate sia a livello di pratica clinica che di politica sanitaria
- Gestione del paziente

STUDI OSSERVAZIONALI CONS

- Bias di selezione
- Elevate percentuali di pazienti persi al FU
- Gestione del paziente
- Valutazione degli esiti (consapevolezza sia del medico che del paziente del trattamento assegnato)

FARMACOVIGILANZA

- Anche dopo l' approvazione dell' AIFA sicurezza ed efficacia continuano ad essere monitorate mediante un processo di Farmacovigilanza teso "all' identificazione, valutazione, comprensione e prevenzione degli effetti avversi o di qualsiasi altro problema correlato all' uso dei medicinali, al fine di assicurare un rapporto beneficio/rischio favorevole per la popolazione"

AIFA, Farmacovigilanza 13/2/2018

Innovazione e sostenibilità

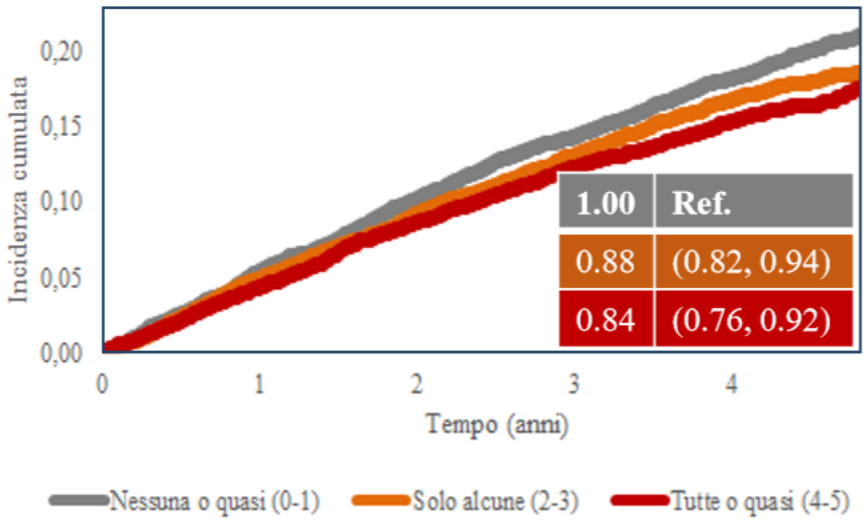
Nuovi modelli assistenziali

Raccomandazioni — Aderenza alle raccomandazioni

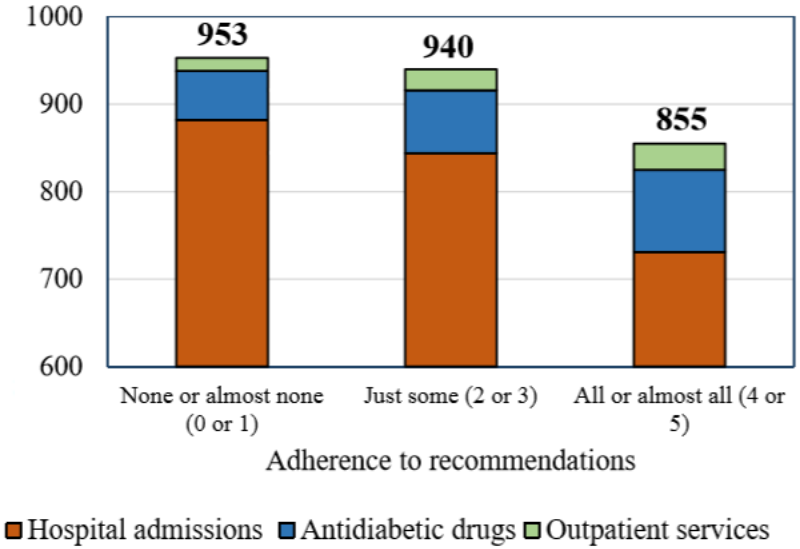
		Lombardia	Friuli Venezia Giulia	Emilia-Romagna	Lazio	Sicilia
tazione e inica	Profilo lipidico[1]	**55.4%**	50.6%	54.2%	46.0%	56.4%
	Funzionalità renale[1,3]	**60.7%**	60.5%	63.7%	56.9%	40.5%
	Emoglobina glicata[2]	**39.8%**	34.8%	36.8%	23.8%	33.3%
	Microalbuminuria[1]	**34.4%**	26.6%	38.0%	19.3%	24.7%
	Esame fondo oculare[1]	**12.1%**	14.5%	22.5%	15.7%	11.5%

1. Almeno un controllo nel primo anno dalla presa in carico
2. Almeno due controlli nel primo anno dalla presa in carico
3. Filtrato glomerulare o creatinina o clearence creatinina

Aderenza alle raccomandazioni e rischio di complicanze [a]



Aderenza alle raccomandazioni e costi a carico del SSN (€ / anno/persona)



[a] Esito composito: Ricovero per Scompenso cardiaco, Infarto miocardico, Patologia cerebrovascolare, Aritmia, Vasculopatia periferica, Complicanze arti inferiori, Procedure di rivascolarizzazione, Diabete con complicanze renali, oculari, neurologiche, circolatorie periferiche, altre complicanze specificate e non

Il confronto tra categorie di aderenza è effettuato con un disegno **Propensity Score Matching**

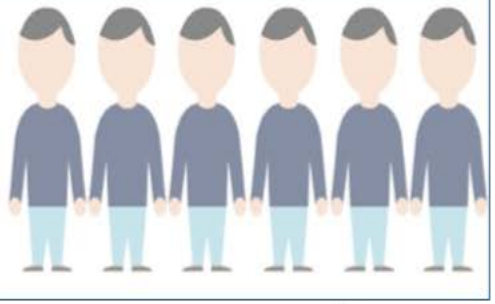
What is 'Real Life' Data?

- Non interventional drug study
- Conducted to assess safety, tolerability and effectiveness of marketed medicines in clinical practice, and in line with the current standard of practice.
- The choice of therapy is consistent with approved marketing authorization
- The diagnostic or monitoring procedures are those applied per the usual treatment paradigm.

Esempi

Cosa manca

Controlled setting



Standard
(linee guida, raccomandazioni)

Real world

Cure
(**monitoraggio** / appropriatezza, accessibilità, processo)

Esiti
(**valutazione** / impatto clinico e sostenibilità delle cure)

Dal funzionamento del SSN …

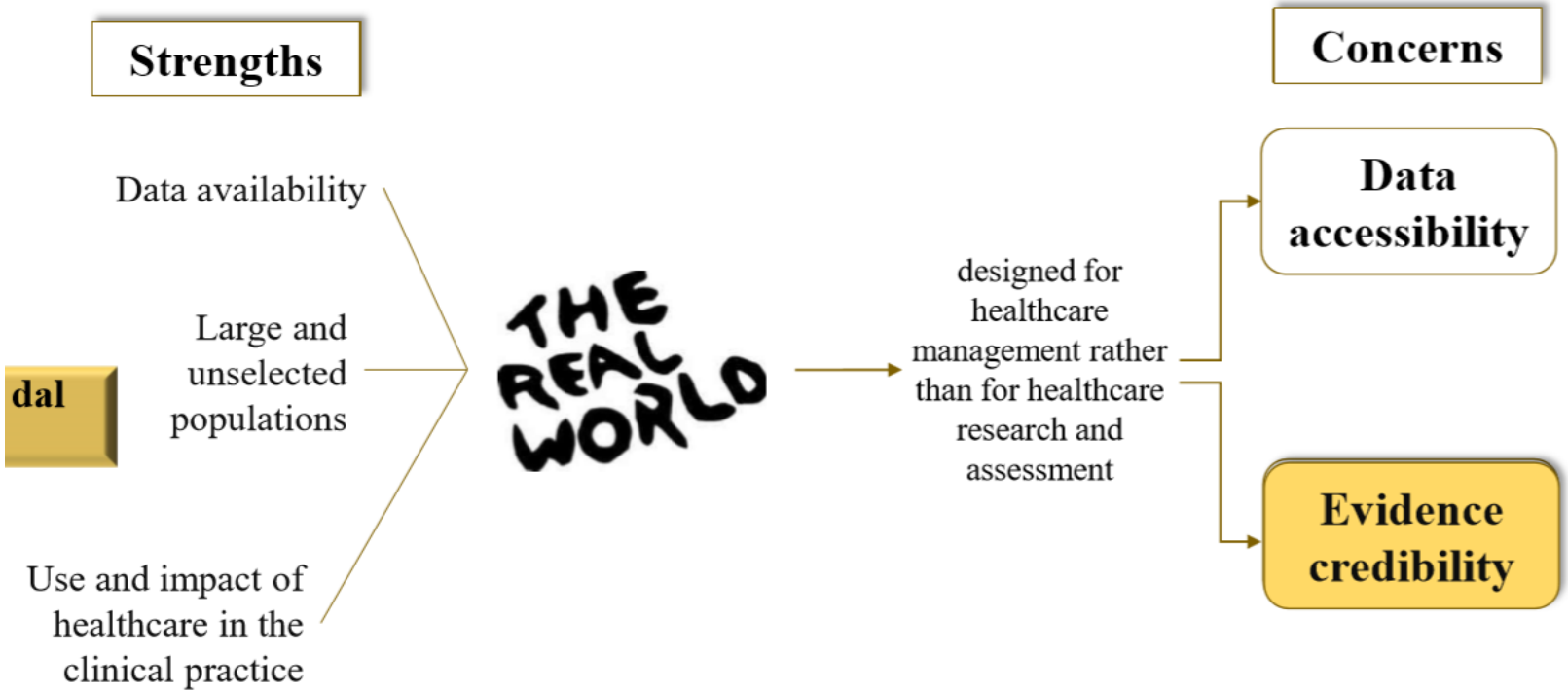
Disponibilità di dati dal mondo reale

Dai RWD alle RWE [a]

… al monitoraggio dei percorsi assistenziali

Disponibilità di dati dal mondo reale

Dai RWD alle RWE [a]


Strengths
Concerns
Data availability
Large and unselected populations
Use and impact of healthcare in the clinical practice
dal
THE REAL WORLD
designed for healthcare management rather than for healthcare research and assessment
Data accessibility
Evidence credibility

La valutazione dei percorsi nel mondo reale

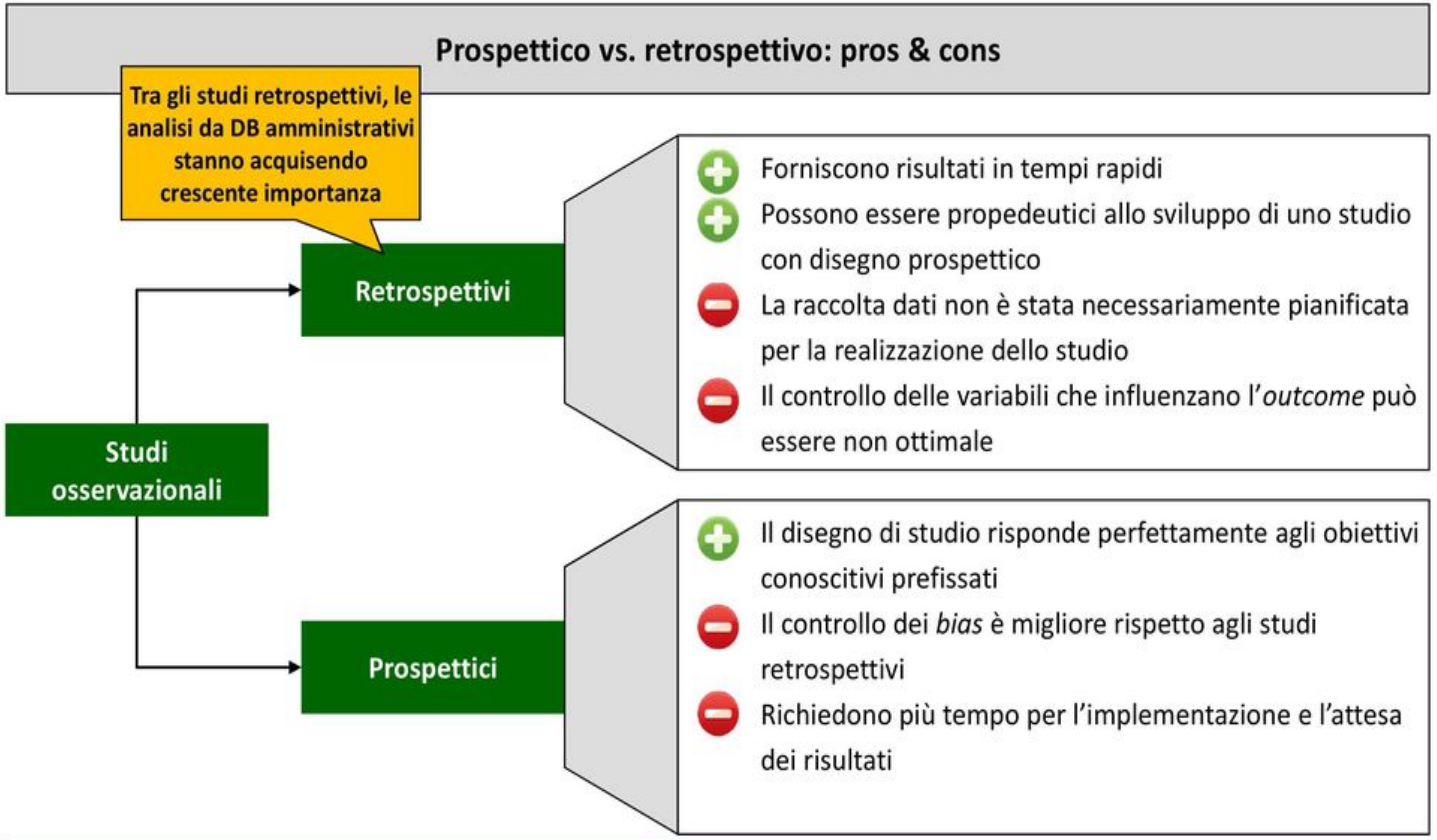
- **non è certamente alternativa, bensì complementare sia alla valutazione degli interventi medici mediante RCT che alla valutazione dell'assistenza centrata sui servizi;**
- **è centrata sul cittadino (patient-centered) implicando l'analisi dell'intera storia dei contatti (PDTA) di ogni singolo cittadino con le prestazioni fornite dal SSN;**
- **offre un certo grado di versatilità**
  - I) adattandosi alla valutazione della singola cura, così come dell'intero PDTA,
  - II) declinando la valutazione in termini di appropriatezza del processo terapeutico erogato, così come di impatto del percorso sui benefici clinici osservati,
  - III) riconoscendo come implicito riferimento la sostenibilità economica del sistema

Dati e fonti dal mondo reale

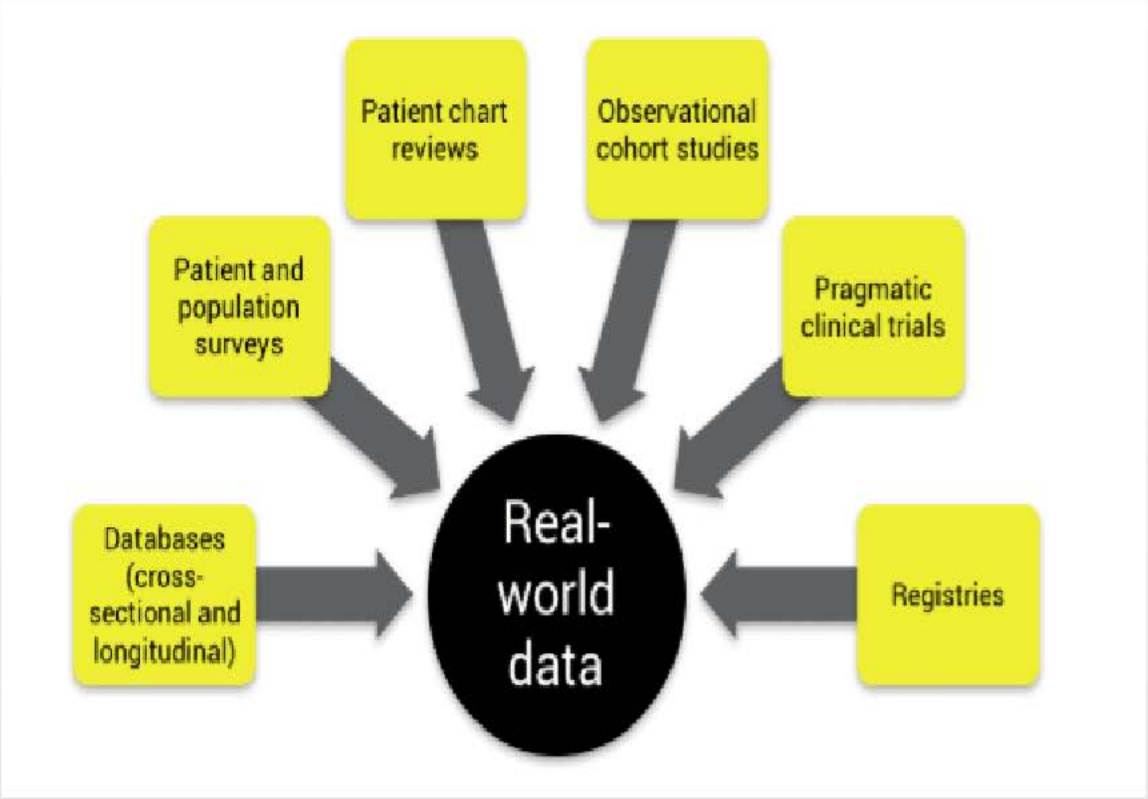
Le definizioni di RWD sono molteplici e non sempre consistenti. Ad esempio, l'International Society for Pharmacoeconomics and Outcomes Research (ISPOR) definisce i RWD come caratterizzati dal fatto "*che vengono raccolti fuori dagli studi clinici controllati interventistici tradizionali nelle circostanze di vita reale*".

Gli studi osservazionali retrospettivi, pur presentando alcuni limiti metodologici, permettono di ottenere informazioni in tempi rapidi

I DB amministrativi sono diventati rilevanti fonti d'informazione per i payers.



Real World Data




WELCOME
TO THE REAL WORLD

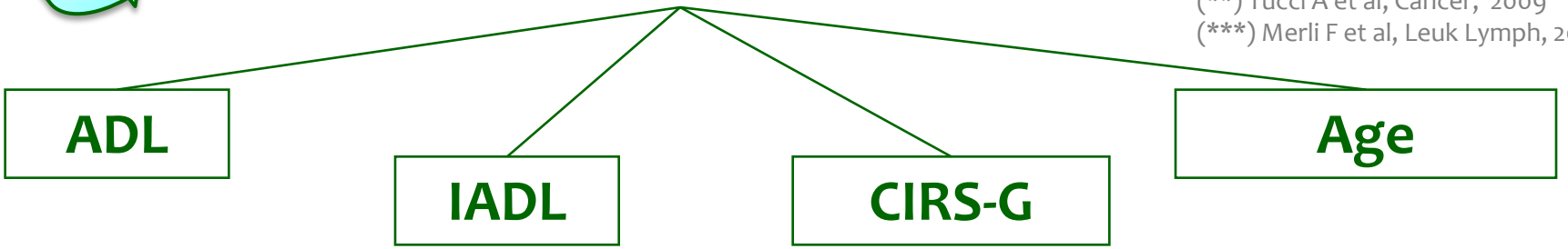
Geriatric Assessment: the FIL Strategy

Modified score originally proposed by Balducci (*)

Validation in a small population of elderly DLBCL (**, ***)

(*) Balducci L et al, The Oncologist, 2000
(**) Tucci A et al, Cancer, 2009
(***) Merli F et al, Leuk Lymph, 2013

"FIL Version" of CGA



	FIT	UNFIT	FRAIL
ADL	6	5*	≤ 4*
IADL	8	7-6*	≤ 5*
CIRS-G	0 of score 3-4 <5 of score 2	0 of score 3-4 5-8 of score 2	1 of score 3-4 > 8 of score 2
Age	-	≥ 80 FIT	≥ 80 UNFIT

*** Residual Functions**

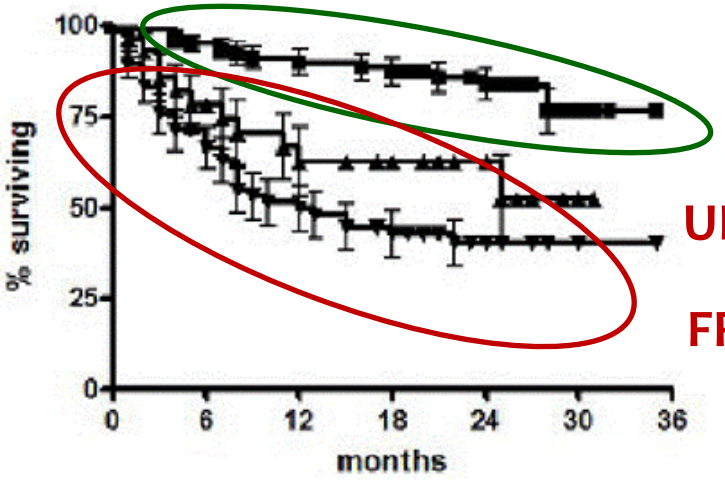
The FIL Experience: Pilot Study

Comprehensive geriatric assessment is an essential tool to support treatment decisions in elderly patients with diffuse large B-cell lymphoma: a prospective multicenter evaluation in 173 patients by the Lymphoma Italian Foundation (FIL)

Tucci A. et al, Leuk Lymph, 2014

prospective multicenter observational study

median follow up: 24 months



FIT **84%**

UNFIT + FRAIL **47%**

p<0.0001

2-year OS UNFIT vs FRAIL *p= ns*

- CGA is a valid tool to identify elderly DLBCL who can benefit from a curative approach.
- CGA is potentially useful to identify different risk groups among NON-FIT patients.
- A proportion of UNFIT pts may benefit significantly if treated with curative intent *(clinical trials should be planned)*.
- Palliation seems the best choice for frail patients

Elderly Project:
Prospective Observational Study

www.filinf.it

< 10 minutes

FIT

full dose therapy

Curative Intent

UNFIT

adapted dose therapy

Curative Intent –

Low Toxicity

FRAIL

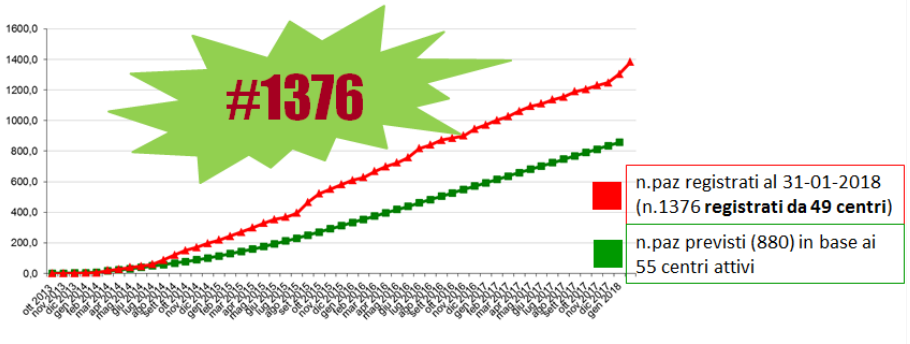
Palliation

Quality of Life

Raccolta prospettica di dati di pazienti anziani (≥ 65 anni)
con Linfoma Diffuso a Grandi Cellule B (DLBCL)
sottoposti al momento della diagnosi
a Valutazione Geriatrica Multidimensionale (VGM)

ID study: Elderly Project

Elderly Project Registrazioni (31-01-2018)



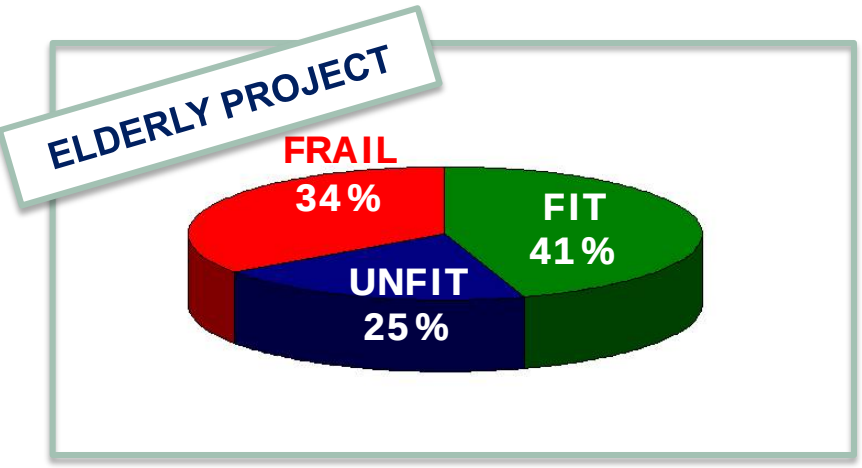
Elderly Project: Clinical Characteristics (N=1237)

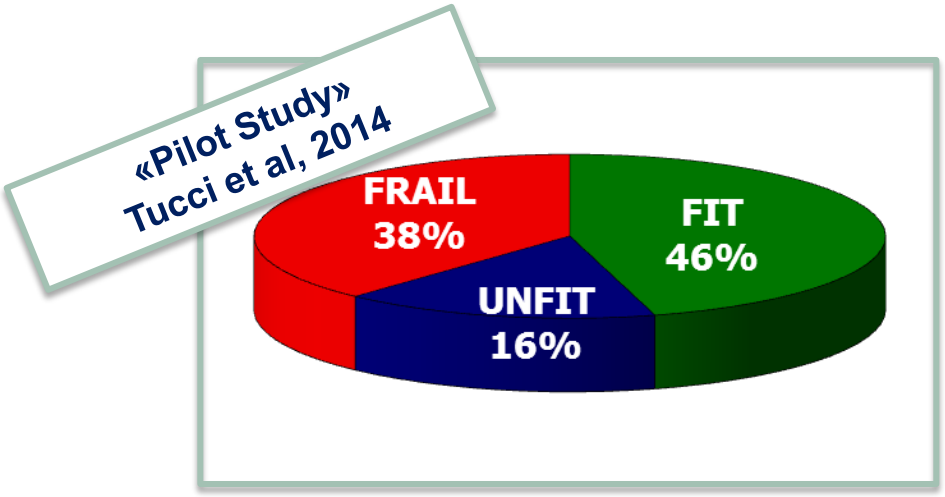
Variable	N (%)	Note
Median age (range)	76 (65-94)	
Age ≥ 80	403 (33%)	
Gender M	631 (51%)	
Stage III-IV	826 (67%)	*missing 12 (1%)*
BM +	166 (19%)	*missing: 342 (28%)*
ENS>1	303 (27%)	*missing: 118 (10%)*
PS >1	251 (20%)	
LDH >UNL	607 (55%)	*missing 131 (11%)*
B-symptoms	322 (26%)	
Bulky Disease	351 (30%)	*missing: 83 (7%)*

Variable	N (%)
IPI	
1	191 (18%)
2	281 (26%)
3-5	595 (56%)
missing / non calcolc.	*170 (14%)*

Elderly Project: Fitness (N=1237)

	ELDERLY PROJECT (31-01-2018)	«Pilot Study » Tucci et al, 2014
Cathegory	*N. (%)*	*N. (%)*
FIT	504 (41%)	79 (46%)
UNFIT	315 (25%)	28 (16%)
FRAIL	418 (34%)	66 (38%)
Total	1237 (100%)	173 (100%)





Elderly Project: Type of Treatment (n = 1115)

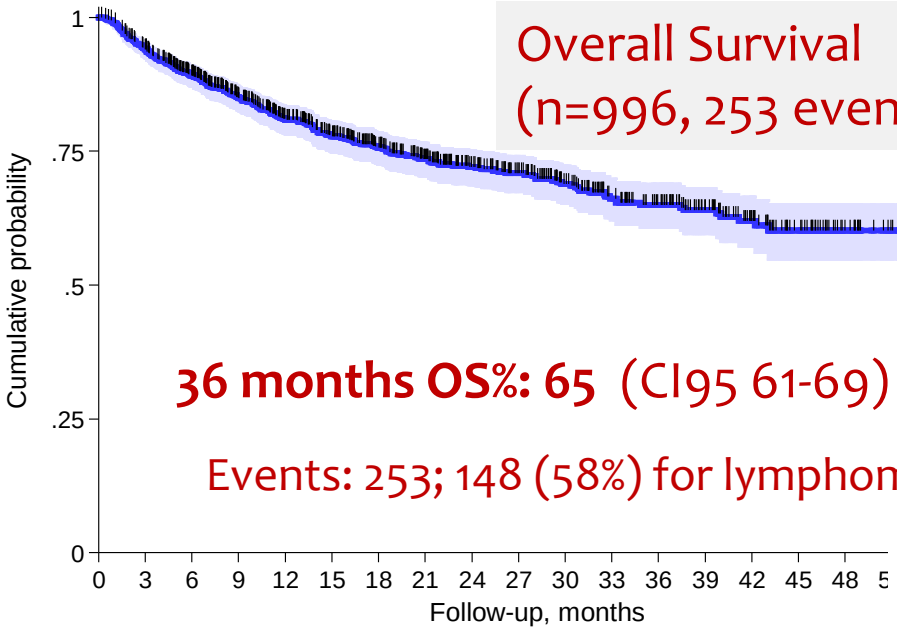
(preliminary data)

Factor	Type, N (%)			Total, N (%)
	FIT (#504) N (%)	UNFIT (#315) N (%)	FRAIL (#418) N (%)	
R-CHOP	279 (60)	50 (17)	42 (12)	371 (33)
R-COMP	127 (27)	90 (31)	81 (22)	298 (27)
R-Other curative	13 (3%)	19 (6)	23 (6)	55 (5)
R-miniCHOP/COMP	39 (8)	105 (36)	95 (27)	239 (21)
R-CVP	1 (<1)	9 (3)	39 (11)	49 (4)
R-Other reduced	3 (1)	5 (2)	9 (3)	17 (2)
R-Benda	-	2 (1)	13 (4)	15 (1)
R-Other palliative	-	5 (2)	19 (5)	24 (2)
Other *(palliative)* - No rituximab	2 (<1)	8 (3)	37 (10)	47 (4)
Total	464	293	358	1115

Elderly Project: Outcome (n = 996)

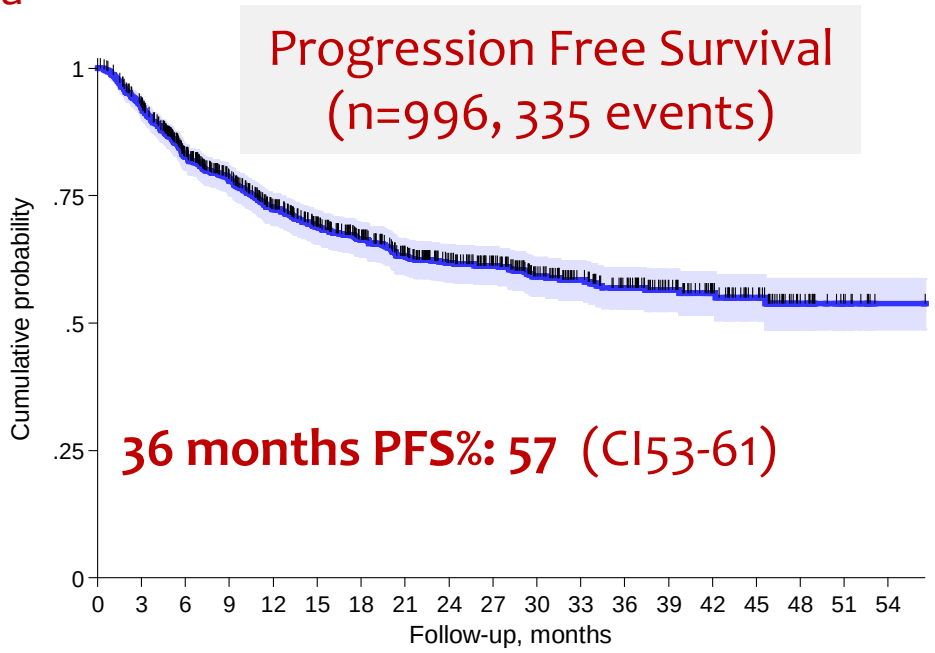
(preliminary data)

Median follow-up: 24 months (range 0.5-56 months)



36 months OS%: 65 (CI95 61-69)

Events: 253; 148 (58%) for lymphoma



36 months PFS%: 57 (CI53-61)

Chronic Lymphocytic Leukemia

ARTICLE

Efficacy of bendamustine and rituximab as first salvage treatment in chronic lymphocytic leukemia and indirect comparison with ibrutinib: a GIMEMA, ERIC and UK CLL FORUM study

Antonio Cuneo,[1] George Follows,[2] Gian Matteo Rigolin,[1] Alfonso Piciocchi,[3] Alessandra Tedeschi,[4] Livio Trentin,[5] Angeles Medina Perez,[6] Marta Coscia,[7] Luca Laurenti,[8] Gerardo Musuraca,[9] Lucia Farina,[10] Alfredo Rivas Delgado,[11] Ester Maria Orlandi,[12] Piero Galieni,[13] Francesca Romana Mauro,[14] Carlo Visco,[15] Angela Amendola,[16] Atto Billio,[17] Roberto Marasca,[18] Annalisa Chiarenza,[19] Vittorio Meneghini,[20] Fiorella Ilariucci,[21] Monia Marchetti,[22] Stefano Molica,[23] Francesca Re,[24] Gianluca Gaidano,[25] Marcos Gonzalez,[26] Francesco Forconi,[27] Stefania Ciolli,[28] Agostino Cortelezzi,[29] Marco Montillo,[4] Lukas Smolej,[30] Anna Schuh,[31] Toby A. Eyre,[32] Ben Kennedy,[33] Kris M. Bowles,[34] Marco Vignetti,[3] Javier de la Serna,[35] Carol Moreno,[36] Robin Foà[14] and Paolo Ghia[37] on behalf of the GIMEMA, European Research Initiative on CLL (ERIC) and UK CLL forum

EUROPEAN HEMATOLOGY ASSOCIATION

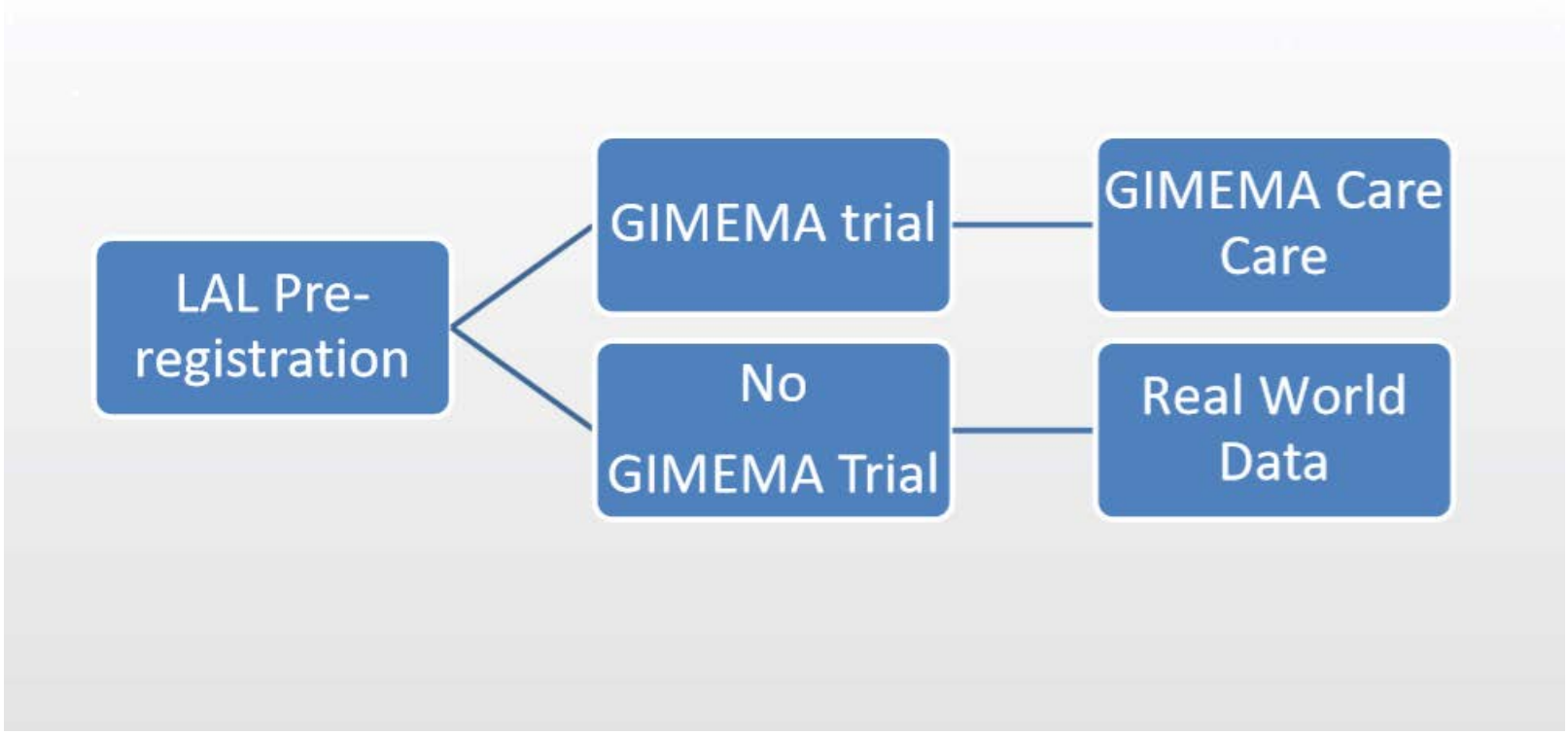
Ferrata Storti Foundation

Haematologica 2018
Volume 103(7):1209-1217

Abstract

Go to:

We performed an observational study on the efficacy of ben-damustine and rituximab (BR) as first salvage regimen in chronic lymphocytic leukemia (CLL). In an intention-to-treat analysis including 237 patients, the median progression-free survival (PFS) was 25 months. The presence of del(17p), unmutated IGHV and advanced stage were associated with a shorter PFS at multivariate analysis. The median time-to-next treatment was 31.3 months. Front-line treatment with a chemoimmunotherapy regimen was the only predictive factor for a shorter time to next treatment at multivariate analysis. The median overall survival (OS) was 74.5 months. Advanced disease stage (i.e. Rai stage III-IV or Binet stage C) and resistant disease were the only parameters significantly associated with a shorter OS. Grade 3-5 infections were recorded in 6.3% of patients. A matched-adjusted indirect comparison with ibrutinib given second-line within Named Patient Programs in the United Kingdom and in Italy was carried out with OS as objective end point. When restricting the analysis to patients with intact 17p who had received chemoimmunotherapy in first line, there was no difference in OS between patients treated with ibrutinib (63% alive at 36 months) and patients treated with BR (74.4% alive at 36 months). BR is an efficacious first salvage regimen in CLL in a real-life population, including the elderly and unfit patients. BR and ibrutinib may be equally effective in terms of OS when used as first salvage treatment in patients without 17p deletion.


LAL Pre-registration
GIMEMA trial
No GIMEMA Trial
GIMEMA Care Care
Real World Data

Gimema Registry of Conception/Pregnancy in Adult Italian Patients Diagnosed with Chronic Myeloid Leukemia (CML)

Background. The availability of multiple tyrosine kinase inhibitors (TKIs) and precise molecular monitoring has dramatically changed the prognosis in CML patients. With proper medical management, the planning of a pregnancy in both male (M) and female (F) patients is now possible. Towards this goal, the GIMEMA CML working party initiated a retrospective and prospective study to describe all male conceptions/female pregnancy outcomes in the CML Italian population from January 2013.

Aims. The specific aims of this study were **to analyze conceptions and pregnancies in male and female patients** with regard to 3 general issues: 1) Illness issues, including CML treatment prior to conception/during/after pregnancy, transcript kinetics, the recovery of a lost response after therapy cessation, and the effects of treatment modifications (e.g., resistance, switching); 2) Conception/pregnancy issues, including planned, unplanned, spontaneous and medically assisted pregnancies (MAP), spontaneous/elective abortions, pregnancy progression, delivery, and breast feeding; and , 3) Post-natal health issues from birth to walking including speaking and academic performance.

Relevance and use of immunoglobulins in the real-world clinical management of patients with chronic lymphocytic leukemia (CLL) in Italy: a GIMEMA survey

In order to better define the clinical relevance of HGG and the use of Ig support in the management of CLL patients in Italy, hematologists from GIMEMA centers will be invited to answer an anonymous online questionnaire

Endpoints:

1. The rate of GIMEMA centers that usually check serum Ig levels in CLL patients.
2. The rate of GIMEMA centers that support HGG CLL patients
3. Criteria addressing Ig support in CLL patients.
4. The preferred type of Ig (iv or sc) utilized in CLL patients

CONCLUSIONI

Inquadramento generale

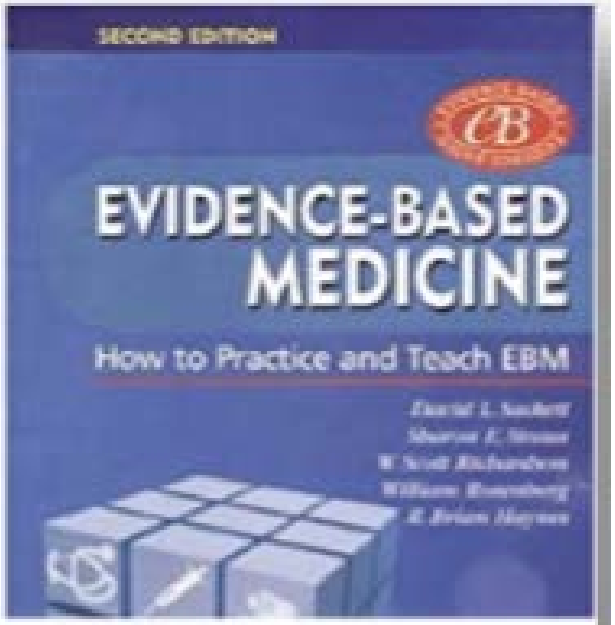
1. **Valutazione degli interventi medici**
   - per la registrazione di un nuovo presidio terapeutico l'ente regolatorio deve necessariamente richiedere il sostegno di solide evidenze di efficacia e sicurezza, e in questo gli RCT non trovano valide alternative

2. **Valutazione dell'assistenza sanitaria**
   - per l'accreditamento e la valutazione di un ente erogatore, il SSN deve necessariamente accertarne la qualità misurandone caratteristiche strutturali e di processo

3. **Valutazione dei percorsi nel mondo reale**
   - gli RCT non sono in grado di prevedere l'impatto degli interventi terapeutici nella pratica clinica
   - oltre che la qualità del singolo erogatore, l'attenzione del SSN deve essere rivolta al cittadino (il beneficiario del SSN) preso in carico perché portatore di un bisogno, valutando l'appropriatezza dell'intero percorso diagnostico-terapeutico-assistenziale (PDTA), la sua utilità (per il paziente) e sostenibilità (per il SSN).

3 valutazioni inquadrate in 3 parole chiave

- **Ricerca clinica**
- **Sanità pubblica**
- **Real World Evidence (RWE):**
  - basandosi sull'esperienza passata dei pazienti in termini di cure ricevute ed esiti osservati nel mondo reale, è in grado di produrre evidenze "credibili" sul modo migliore per trattare i pazienti nel futuro.
  - per produrre RWE è necessario disporre di dati tratti dal mondo reale (d'ora in avanti RWD da Real World Data).



"... If you find that a study was not randomized, we'd suggest that you stop reading it and go to the next article ..."

The NEW ENGLAND JOURNAL of MEDICINE

1993;329:1196-9

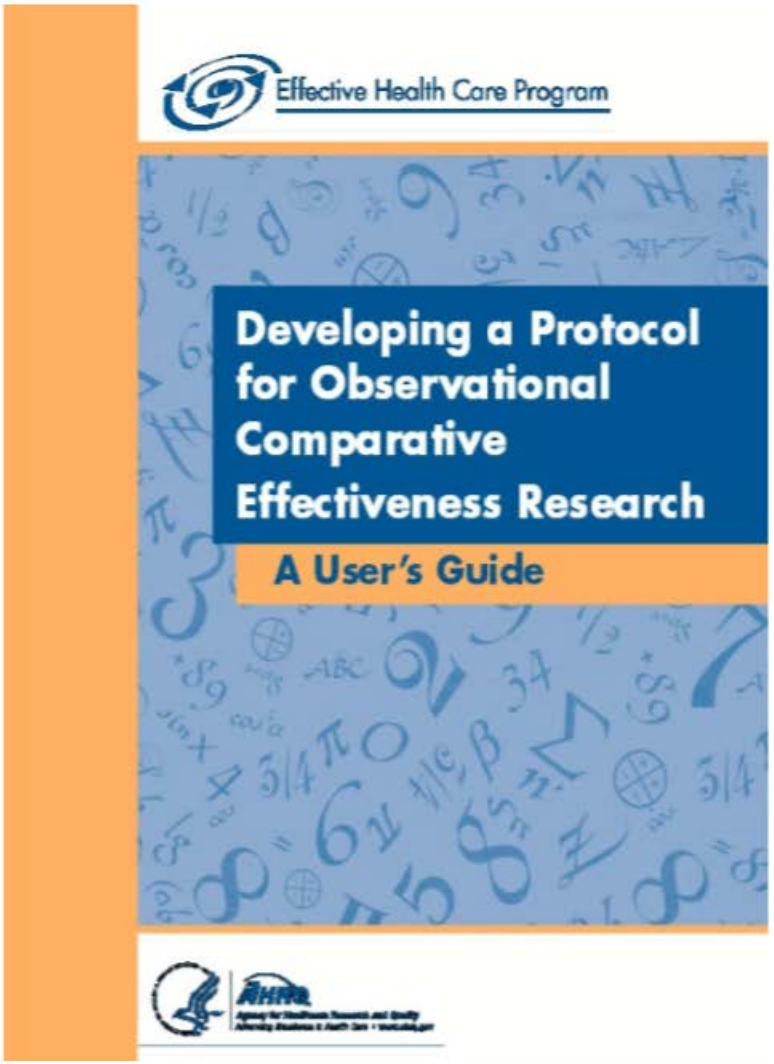
Data Torturing

"If you torture your data long enough,
they will tell you whatever you want to hear"

Il paradigma della ricerca clinica non è cambiato, deve essere «solo» adattato al nuovo contesto

Per generare evidenze credibili bisogna adottare e diffondere norme condivise per la buona pratica della ricerca (clinica) osservazionale con fonti secondarie

Velentgas P, Dreyer NA, Nourjah P, Smith SR, Torchia MM, eds Agency for Healthcare Research and Quality. January 2013



Real World Data

- i dati (RWD) sono semplici materie prime da sole non informative, l'evidenza (RWE) presuppone l'organizzazione dei dati stessi e il loro trattamento secondo un piano di ricerca predefinito (protocollo) e la conseguente presentazione e interpretazione dei metodi e dei risultati in un documento (report).

- Le reti di Centri di Ematologia vengono utilizzate per fare ricerca clinica con grande successo
- Possono offrire grandi opportunità per generare REAL WORLD DATA e così produrre REAL WORLD EVIDENCE in Ematologia
- E' necessario adeguare quindi il proprio approccio culturale all' importanza della raccolta dei dati della realtà clinica di tutti i giorni.

Grazie per l’ attenzione

Asl BAT
BARLETTA-ANDRIA-TRANI

Rete Ematologica Pugliese